UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/019,693	01/03/2002	Naoyuki Koizumi	2001-1930A	1850

513 7590 07/02/2003

WENDEROTH, LIND & PONACK, L.L.P.
2033 K STREET N. W.
SUITE 800
WASHINGTON, DC 20006-1021

EXAMINER	
PATEL, SUDHAKER B	
ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 07/02/2003

7

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/019,693	KOIZUMI ET AL.	
	Examiner	Art Unit	
	Sudhaker B. Patel, D.Sc.Tech.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *2,4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicants' communication paper # 6 dated 6/2/03 is acknowledged.

Election/Restrictions

1. Because applicants did not distinctly and specifically point out the supposed errors in the restriction/election requirement, the election has been treated as an election without traverse (MPEP 818.03(a)).

Applicants have elected invention of Group I, claims (in part) 1-17 drawn to compounds, compositions, method of use for the generic Formula (I) wherein components A and R3 are not forming a tricyclic ring, and have also elected species of compound of Example 27 as recited in page 30 lines 10-19 of the specification, namely, 2',4'-dicyanobiphenyl-4-yl-sulfamate.

Applicants are reminded of the election of species guidelines provided in MPEP 803.02, which are followed for the examination.

The elected species of compound of Example 27 as stated earlier has following meanings for variables in the generic Formula (I) of claim 1:

A and R3	= Not forming a fusion to provide a tricyclic ring;
A	= 2,4-dicyano –Phenyl;
A	= Occupies position 4- on phenyl with para-O-SO2NH2;
R1	=H;
R2	=H;
R3	=H;
-O-SO2-N(R1)(R2)	=--O-SO2NH2.

Initial search with above definitions of the variables for the species did not reveal prior art. Therefore, the search was expanded to invention of Group I wherein:

A and R3	= Not forming a fusion to provide a tricyclic ring;
A	=-Phenyl substituted or unsubstituted ;
A	=--X-NR4R5 wherein X=CO;R4/R5=(H)/phenyl ;
A	= Occupies position 4- on phenyl;
R1	=H or lower alkyl group;
R2	=H or lower alkyl group;
R3	=H or lower alkyl, NO2, CN;
-O-SO2-N(R1)(R2)	=--O-SO2N-(H)2 or -(alkyl)2, and

art(s) was found (see rejections bellow.

Search was limited to meanings of variables as stated above. All other definitions of variables than stated above are excluded from further consideration. 37 CFR 1.142(b).

This application has been found to contain more than one invention. Therefore, the requirement is still deemed proper and is therefore made FINAL.

First action on merits follows.

Priority

2. Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Japan on 7/6/19999. It is noted, however, that applicant has not filed a certified copy of the JP 11/191632 application as required by 35 U.S.C. 119(b).

Claim Rejections - 35 USC § 101

3. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 15,17 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a step or process asserted utility or a well established utility.

The claim 15 is related to use of a compound of claim 1 for treatment as well prophylaxis of diseases wherein the steps are unknown.

Claim 17 recites the use of compounds of claim 1 for preparati0on of an agent for treatment of diseases. The process of making an agent and the steps involved are not known.

Claims 15,17 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a step or process of prophylaxis or process of making asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Following reasons apply.

(A). Claims 1-17 recite: " A phenyl sulfamate derivative or salt thereof". It is open ended because it includes other compounds not claimed herein also. "Sulphamate is an ester of a sulfamic acid as well as salt of sulphamic acid. Also, " salt" as recited is not very specific. Correction to: " A compound of Formula (I) or its pharmaceutically acceptable salts" is required.

(B). In claim 1, line 2 sentence is ending with: "salt thereof."., and a second sentence is starting with: "wherein". The verb in the second sentence is missing. Correction is required.

Claim Objections

6. Claims 12,13 are objected to under 37 CFR 1.75 as being a substantial duplicate of claim 14. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 16 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating human breast cancer, does not reasonably provide enablement for prophylaxis of other diseases as recited herein. The specification does not enable any person skilled in the art to which it pertains, or with

which it is most nearly connected, to practice the invention commensurate in scope with these claims. The diseases include endometrial hyperplasis, infertility, demantia, Alzheimer's; disease, corpus uteri cancer, autoimmune diseases and diseases yet not discovered.

In evaluating the enablement question, several factors are to be considered. In re Wands, 8 USPQ 2d 1400 (Fed. Cir. 1988); Ex parte Forman, 230 USPQ 546. The factors include:***(1).*** The nature of invention;***(2).*** the state of prior art ;***(3).*** the predictability or lack thereof in the art;***(4).*** the amount of direction or guidance present;***(5).*** the presence or absence of working examples;***(6).*** the breadth of the claims, and ***(7).*** the quantity of experimentation needed.

Discussion about AD:

1) The nature of the invention: The method of use claims are drawn in part to prophylaxis and treating of diseases caused by steroid sulfatase. The diseases include in addition to cancer(s),dementia, infertility, Alzheimer's disease, autoimmune diseases, and many others as recited herein.

2) The state of the prior art: There are no known compounds of similar structure which have been demonstrated to treat Alzheimer's disease nor is there any compound that can be used to treat excess dietary alcohol intake, diabetes, cerebral and myocardial ischemia and other diseases by a single compound. For example, the notion that a compound could be effective against chemical substance abuse or withdrawal caused by the cessation of intake of chemical substances in general is absolutely contrary to our current understanding of how chemical dependencies operate. There is not, and probably never will be, a pharmacological treatment for "chemical substance abuse or withdrawal caused by the cessation of intake of chemical substances" generally. That is because "chemical substance/alcohol abuse or withdrawal caused by the cessation of intake of chemical substances" is not a single disease or cluster of related disorders, but in fact, a collection with relatively little in common. Addiction to barbiturates, alcohol, cocaine, opiates, amphetamines, benzodiazepines, nicotine, etc. all involve different parts of the CNS system; different receptors in the body. For example, cocaine binds at the dopamine reuptake transmitter. Heroin addiction, for example, arises from binding at the opiate receptors, cigarette addiction from some interaction at the nicotinic acid receptors, many tranquilizers involve the benzodiazepine receptor, alcohol involves yet another system, etc. All attempts to find an pharmaceutical to treat chemical addictions generally have thus failed. Alzheimer's disease is treated, albeit not successfully, using acetylcholine esterase inhibitors and Parkinson's disease using dopamine receptors. A disease in the central or peripheral system is not a single disease but embraces disease that are not related or even "opposites".

3) The predictability or lack thereof in the art: It is presumed in the treatment of the diseases claimed herein there is a way of identifying any and all of the diseases which

are responsive to the activity of steroid sulfatase inhibitors. There is no evidence of record which would enable the skilled artisan in the identification of the diseases treatable with the disorders claimed herein.
4) The amount of direction or guidance present and 5) the presence or absence of working examples: There are no doses present for treatment of the disorders recited.
6) The breadth of the claims: The claims are drawn to disorders that are not related and whose treatment is unknown.
7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan for the many reasons stated above.

Following references are cited to show the state of art related to a few of the diseases recited herein:

Understanding about Alzheimer's disease:

Coyle et al(Science Vol.219, pages 1184-1190(1983)) cites in the summary that:" These cholinergic neurons provide widespread innervation of the cerebral cortex and related structures and appear to play an important role in cognitive functions, especially memory". The authors conclude (see page 1189) that:" The identification of a transmitter-specific pathway selectively affected in a major form of dementia is an important step in the design of diagnostic studies, investigations of pathogenic mechanisms, and the development of therapeutic approaches to these debilitating neuropsychiatric disorders".

Discussion about cancer(s):

For example, the claim sets forth not only for the treating human breast cancer but also for prophylaxis of endometrial hyperplasis, infertility, demantia, Alzheimer's; disease, corpus uteri cancer, autoimmune diseases and diseases yet not discovered generally. However, there never has been a compound capable of treating various types of cancers. There are compounds that treat a range of cancers, but no one has ever been able to figure out how to get a compound to be effective against cancers and pain as recited earlier, or even a majority of cancers. Thus, the existence of such a "silver bullet" is contrary to our present understanding in oncology. Even the most broadly effective anti-cancer agents are only effective against a small fraction of the vast number of different cancers known. This is true in part because cancers arise from a wide variety of sources, such as viruses (e.g. EBV, HHV-8, and HTLV-1), exposure to

chemicals such as tobacco tars, genetic disorders, ionizing radiation, and a wide variety of failures of the body's cell growth regulatory mechanisms. Different types of cancers affect different organs and have different methods of growth and harm to the body, and different vulnerabilities. Thus, it is beyond the skill of oncologist today to get an agent to be effective against cancers generally, evidence that the level of skill in this art is low relative to the difficulty of such a task. This is only for one of the many disorders as claimed herein.

Following references are quoted to show the state of art:

- ***Cecil Textbook of Medicine*** states that: " each specific type of cancer has unique biological and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). Different types of cancers affect different organs and have different methods of growth and harm to the body. Also see In re Butting, 163, USPQ 689 (CCPA 1969), wherein "evidence involving a single compound and two types of cancer, was held insufficient to establish the utility of the claims directed to disparate types of cancers".

Structure-Based Design of Novel Anticancer Agent:
Uckun et al(see Current Cancer Drug Targets, 1,59-71(2001) concludes in pages 66-67 that : " WHI-P131, which inhibits JAK3 but does not inhibit JAK1, JAK2, SYK,BTK,LYN or IRP even at concentrations as high as 350uM is undergoing further studies to evaluate its potential use as a new anti leukemic agent(in children). Agents that inhibit epidermal growth factor receptor(EGFR) may be useful for treatment of breast cancer. Tubulin modulating agents, which are of natural as well as synthetic origin, can be used as effective anticancer agents for treating breast cancer.COBRA compounds caused destruction of microtubule organization and apoptosis. Like other microtubule-interfering agents, COBRA compounds activated the proapoptotic c-Jun N-terminal kinase (JNK) signal transduction pathway, as evidenced by rapid induction of c-jun expression".

Specification on pages 19-22 recite various methods of assays and tests carried out "In vitro" and " In vivo" for instant compounds, and Table I on page 20 recites the "

In Vitro" comparative results for 4 of the instant compounds without currently available references.

The results provided for inhibitory rate as: (3 x 10 –9 M, %), are having a range of 67 – 94 .

The " In vivo" efficacy test results as recited in Table 2 on page 21, exhibit the performance of 6 selected compounds only. There is no comparison similar to "In vitro" results for the elected species of compound of Example 27, and art recognized reference sample(s). The results for "rats" as models are recited as:

Inhibitory rate(0.5 mg/Kg. p.o., %):

- For Liver the range is 85.3 – 99.5 %;
- For Uterus the range is 79.o – 100%.

These results are not sufficient to support the methods of use claims claiming treating of various cancers, Alzheimer' disease, fertility, autoimmune diseases and other disease as recited herein. These results will help as preliminary guideline for screening the compounds only.

Statements of utility, which relate to or imply to treatment of a disease are subject to closer scrutiny. Ex parte Moore et al.(POBA 1960) 128 USPQ 8. Claim 16 does not meet the Utility Guidelines. The claims do not qualify as one utility statement, and are not believable on their face. Claims will require too much experimentation to determine what patient dosage relationship would produce what results. It is not believable on its face that any one compound would have all of those utilities. In re Hozumi, 226 USPQ 353.

Evidence involving a single compound and two types of cancer, was held insufficient to establish the utility of claims directed to a method of treating 7 types of cancer with member of a class of several compounds. In re Buting, (CCPA 1969) 418 F2d 540, 163 USPQ 689.

The instant claims relate not only to treatment of cancer(s), but also to treatment .and prophylaxis of various diseases as recites earlier.

The quantity of experimentation need would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan for the many reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skilled in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims involving use of compounds, their compositions.

When the best efforts have failed to achieve a goal, it is reasonable for the PTO to require evidence that such a goal has been accomplished, *In re Ferens*, 163 USPQ 609. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs. Novo Nordisk*, 42 USPQ2nd 1001, 1006.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1. Claims 1-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Juettner et al(DE 1136687).

The reference compounds have following meanings for the instant variables:

A and R3	= Not forming a fusion to provide a tricyclic ring;
A	=-Phenyl substituted ;
A	= Occupies position 4- on phenyl;
R1	=lower alkyl group;
R2	=H or lower alkyl group;
R3	=H ;
-O-SO2-N(R1)(R2)	=--O-SO2N -(alkyl)2.

The compound having CAS RN # 101547-37-9 (Sulfamic acid, dipropyl-, 4,4'-diphenylylene ester) reads onto instant claims.

2. Claims 1-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Dunbar et al (US 3082238).

The reference compounds have following meanings for the instant variables:

A and R3	= Not forming a fusion to provide a tricyclic ring;
A	=-Phenyl substituted ;
A	= Occupies position 4- on phenyl;
R1	= lower alkyl group;

R2	=lower alkyl group;
R3	=H;
-O-SO2-N(R1)(R2)	=--O-SO2N -(alkyl)2.

The compound having CAS RN # 98176-69-3(= Sulfamic acid, dimethyl-, 4,4-biphenlyylene ester) reads onto instant claims.

3. Claims 1-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Hofogaya (JP 56083467, also cited as Chemical Abstract DN 95:186905).

The reference compounds have following meanings for the instant variables:

A and R3	= Not forming a fusion to provide a tricyclic ring;
A	=--CO-NH-Phenyl substituted(=dihalo substituted) ;
A	= Occupies position 4- on phenyl;
R1	= lower alkyl group;
R2	=H;
R3	=H;
-O-SO2-N(R1)(R2)	=--O-SO2N -(alkyl)2.

The compound having CAS RN # 79603-69-3(= Sulfamic acid, dimethyl-, 4-[[(2,3-dichlorophenyl)amino]carbonyl]phenyl ester) reads on to the instant claims.

Conclusion

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sudhaker B. Patel, D.Sc.Tech. whose telephone number is 703 308 4709. The examiner can normally be reached on 6:30 to 5:00 pm (Monday-Thursday).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Mukund J. Shah can be reached on 703 308 4716 or Sr. Examiner Mr. Richard Raymond at (703) 308 4523.

The fax phone numbers for the organization where this application or proceeding is assigned are 703 308 4556 for regular communications and 703 308 4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 308 1235.

Sudhaker B.Patel, D.Sc.Tech.
June 30, 2003.

MUKUND SHAH
SUPERVISORY PATENT
EXAMINER
ART UNIT 1624